PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Surgical Treatment of Colorectal Cancer: Analysis of the Influence of an Enhanced Recovery Programme on Long-term Oncological Outcomes. Study Protocol for a prospective, multicentre, observational cohort study
AUTHORS	Ramirez-Rodriguez, Jose-M; Martinez-Ubieto, Javier; Muñoz-Rodes, Jose-L; Rodriguez-Fraile, Jose-R; Garcia-Erce, Jose-A; Blanco-Gonzalez, Javier; Del Valle-Hernandez, Emilio; Abad-Gurumeta, Alfredo; Centeno-Robles, Eugenia; Martinez-Perez, Carolina; Leon-Arellano, Miguel; Echazarreta-Gallego, Estibaliz; Elia-Guedea, Manuela; Pascual-Bellosta, Ana; Miranda-Tauler, Elena; Manuel-Vazquez, Alba; Balen-Rivera, Enrique; Alvarez-Martinez, David; Perez-Peña, Jose; Abad-Motos, Ane; Redondo-Villahoz, Elisabeth; Biosta-Perez, Elena; Guadalajara-Labajo, Hector; Ripollés-Melchor, Javier; Latre-Saso, Cristina; Cordoba-Diaz de Laspra, Elena; Sanchez-Guillen, Luis; Cabellos-Olivares, Mercedes; Longas-Valien, Javier; Ortega-Lucea, Sonia; Ocon-Breton, Julia; Arroyo-Sebastian, Antonio; Garcia-Olmo, Damian

VERSION 1 – REVIEW

REVIEWER	Gaëtan-Romain Joliat Department of Visceral Surgery Lausanne University Hospital CHUV Switzerland
REVIEW RETURNED	11-Jun-2020

GENERAL COMMENTS	The authors plan to do a multicenter, observational study on the long-term oncologic outcomes of an ERP in colorectal cancer surgery. The study will take place in 12 hospitals in Spain. Overall the protocol is well presented and clear. English should be checked throughout the protocol. The objectives are clearly defined. Abstract (introduction) and introduction: I would specify that ERAS lowers the response to surgical aggression but not the surgical aggression in itself. As mean/median compliances of all centers will be around 70%, do you think that there will be enough differences in both groups (in the group with compliance >70% and in the group with compliance <70%)? We know that the higher the compliance, the better the outcomes. So in the hospitals with a compliance <70%, one will try to improve the compliance. How are you going to take into account if one center evolves from low compliance to high compliance (>70%)? Statistical analysis:

	- “According to the literature …”, I would add a reference. - Why would you call non-ERAS centers the centers with compliance <70% as they have an ERAS protocol? I would call the groups differently (for example low compliance or high compliance). Dates such as study start or estimated end of the study are missing. Are the ERAS guidelines based on the recommendations of the ERAS® Society? If yes, I would specify it.

REVIEWER	Varut Lohsiriwat Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
REVIEW RETURNED	02-Aug-2020

GENERAL COMMENTS	Thank you for the opportunity to review a study protocol entitled "Surgical Treatment of Colorectal Cancer: Analysis of the Influence of an Enhanced Recovery Programme on Long-term Oncological Outcomes: A prospective, multicentre, observational cohort study leading by J.M. Ramírez-Rodríguez et al. The research question and its primary outcomes is of great interest and importance. The study design is rational and scientifically sound. I have only a few questions: 1) As noted in the inclusion criteria "All adult patients (aged >18 years) with a diagnosis of malignant colorectal cancer who are scheduled for radical surgery.", will stage IV CRC patients with resectable metastasis be included? 2) Regarding the data collection of postoperative complication, Clavien-Dindo classification and/or comprehensive complication index (CCI) may be a beter representative than those described in the protocol as the complications at 60-day follow-up (surgical complications, infectious complications, cardiovascular complications), each rated as mild, moderate, or severe.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1 COMMENTS

1. Abstract (introduction) and introduction: I would specify that ERAS lowers the response to surgical aggression but not the surgical aggression in itself.

We have changed the sentence in abstract (pag. 1) and introduction (pag 2).

2. As mean/median compliances of all centers will be around 70%, do you think that there will be enough differences in both groups (in the group with compliance >70% and in the group with compliance <70%)?

Certainly it is a challenge, however 70% is the level of compliance to consider that an ERAS protocol is adequately implemented and it is the cutting point for statistical analysis of similar studies (references 17 and 19 of the article)

3. We know that the higher the compliance, the better the outcomes. So in the hospitals with a

compliance <70%, one will try to improve the compliance. How are you going to take into account if one center evolves from low compliance to high compliance (>70%)?

We agree with the reviewer about trend of compliance in many centres. However, in our experience with Spanish centres, what is relevant is “sustainability”. For most hospital it is difficult to reach even the 70% of compliance and much more difficult to sustain such rate along the time. Honestly, we do not believe we have to cope with high compliance issues, on the contrary. Having this in mind we included the issue as a potential limitation of the study.

4. Statistical analysis:
“According to the literature …”, I would add a reference.

We have modified the sentence and added the reference (page 4)

5. Why would you call non-ERAS centers the centers with compliance <70% as they have an ERAS protocol? I would call the groups differently (for example low compliance or high compliance).

Absolutely agree, we have modified the name of groups: High-compliance (HC) and Low-compliance (LC).

6. Dates such as study start or estimated end of the study are missing.

The planned date for start and end have been included in the method section under the follow-up paragraph (page 4)

7. Are the ERAS guidelines based on the recommendations of the ERAS® Society? If yes, I would specify it.

ERAS protocols are based on similar or rather similar recommendations. Said this, hospitals in Spain follow the Spanish National Health Service guidelines that were edited in 2015. The English version of such guidelines can be download from: https://portal.guiasalud.es/wp-content/uploads/2019/10/viaclinica-rica_english.pdf (all this specified in pag. 3: setting)

REVIEWER 2 COMMENTS

1) As noted in the inclusion criteria "All adult patients (aged >18 years) with a diagnosis of malignant colorectal cancer who are scheduled for radical surgery.", will stage IV CRC patients with resectable metastasis be included?

This question generated a great debated between us. At the end we decided do not included Stage IV patients due to the fact of the difficulties in measuring the added “surgical stress” (¿how many metastases?.¿advanced surgery, sincronous surgery ?..) that could affect the final study outcome. We have clarified this point in page 3; exclusion criteria)

2. Regarding the data collection of postoperative complication, Clavien-Dindo classification and/or comprehensive complication index (CCI) may be a beter representative than those described in the protocol as the complications at 60-day follow-up (surgical complications, infectious complications, cardiovascular complications), each rated as mild, moderate, or severe.

Thank you very much for the suggestion. We agree with the reviewer and will include the Clavien-Dindo classification in our data collection set. We have modified the paragraph in page 4.

VERSION 2 – REVIEW

REVIEWER	Varut Lohsiriwat Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
REVIEW RETURNED	17-Aug-2020

GENERAL COMMENTS	The authors have properly revised the manuscript according to the reviewers' recommendation and suggestion.